DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Rese
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Certified-Return Receipt Requested

WARNING LETTER

Ms. Betty Castor
President
University of South Florida
4202 East Fowler Avenue
Administration Building, Room 241
Tampa, Florida 33620

Dear Ms. Castor:

During an inspection that concluded on March 4, 1998, Ms. Shari J. Hromyak, an investigator with the Food and Drug Administration (FDA), inspected the University of South Florida Health Science Center Institutional Review Boards (IRBs) #01 and 01B. The purpose of the inspection is to determine if the IRBs' procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

A copy of the list of Inspectional Observations (FDA-483) left with Dr. George R. Newkome at the end of the inspection is enclosed. The deviations noted in our inspection include, but are not limited to the following:

1. **Failure to conduct adequate continuing review of research. [21 CFR 56.109(f)]**

   The IRBs conduct continuing review inappropriately. The current system may not adequately ensure protection of research subjects. For example:

   a. No IRB members review study files for continuing reviews.

   b. All continued review is accomplished by an "expedited" process. The Chair of IRB 01 reads progress reports and forwards recommendations to both IRBs.

c. The IRB members receive only agenda (summarized) information to review for studies due for continued review. The agendas are compiled by the IRB associates not members. The IRB associates select and include information in the agendas from the clinical investigators' progress reports regarding the studies due for continued review.

d. One vote is taken to approve all of the studies due for continuing review as a unit listed on the IRBs' agendas with little, if any, discussion.

e. There is apparently no review of the consent form(s) during the time of study review and renewal.

The methods of continuing review implemented by IRBs 01 and 01B deviate significantly from the federal regulations. The IRBs are responsible for continual monitoring and oversight of investigational drug studies and the protection of research subjects. The IRBs appear to "rubber stamp" studies due for continuing review without full review of the study file as intended by the regulations. This practice is not acceptable.

The purpose of continuing review is to review the entire study, not just changes in it. Continuing review of a study may not be conducted through an expedited review procedure, unless 1) the study was eligible for, and initially reviewed by, an expedited review procedure, or 2) the study has changed such that the only activities remaining are eligible for expedited review.

Studies that accrued subjects during the previous approved time period and were not eligible for expedited review should receive continuing review by the full board. The file should be reviewed examining, at a minimum, any previous progress reports, the number of subjects, the consent form, amendments, and the history of adverse events, if any.

Continuing review should include a reexamination of the consent form to ensure the form contains accurate, current, and adequate information regarding the study, FDA regulations, and information such as the current phone numbers and contacts for answers to research questions, subjects' rights, and the contact for research subject injuries, for example.

2. **Failure to fulfill requirements for expedited review. [21 CFR 56.110]**

The FDA investigator reviewed 12 months of meeting minutes and found <u>all</u> amendments and revisions for approved studies approved via expedited review. For example:

a. The [redacted] memo for IRB study [redacted], dated 3/4/97, required that full IRB approval be obtained for Addendum #3 because of a therapeutic change to the protocol. A letter to the clinical investigator dated 4/15/97 indicates the addendum was approved by expedited review.

b. It appears that IRB study [redacted] received no discussion during IRB meetings for study renewal. The study is listed in IRB 01 meeting minutes as number 47 on 11/6/95 and number 17 on 11/4/96 under Continued Reviews That Have Not Experienced Changes or Adverse Reactions. The study experienced significant changes and at least one adverse event. One on-site adverse event was reported for the study in 7/96. Also, Amendments #4 and 5 involved significant changes in the treatment of subjects. Amendment #4 involved changes from enrolling subjects for random treatment to also permitting new enrollees to select treatment with the test article as a new third arm of the study. Amendment #5, dated 8/15/95, allowed for cross over of subjects into the alternate study drug treatment. There were many changes to the consent form. The study was granted IA (Institutional Approval) which is not defined in the IRB SOPs.

3. **Failure to meet the criteria for IRB membership. [21 CFR 56.107(a)]**

The FDA investigator found that IRB members lacked adequate knowledge of the Institutional Review Board Policies and Procedures (IRB SOPs) or federal regulations regarding expedited review, continued review, and emergency use requirements.

4. **Failure to prepare detailed written procedures for conducting the review of research, including periodic review. [21 CFR 56.108(a), (b), and 56.115(a)(6)]**

At the time of inspection the University of South Florida Health Science Center Institutional Review Board lacked written procedures for the following:

a. Review and approval of "compassionate" or single use requests of test articles.

b. Detailed procedures that describe the primary reviewer system actually used by the IRBs, including the specific documents provided to the primary reviewers and other IRB members.

c. Institutional Approval as noted in some IRB meeting minutes.

d. Definition of "projects without change."

5. **Failure to follow written procedures for conducting continuing review of research. [21 CFR 56.108(a)]**

The IRBs fail to follow written procedures when <u>all</u> studies for continuing review are approved using a review category mentioned but not clearly defined in the IRB SOPs as "projects without change."

6. **Failure to ensure prompt reporting to the IRB of any unanticipated problems involving risks to human subjects or others. [21 CFR 56.108(b)(1)]**

   One on-site adverse event reported for IRB study ~~~ resulted in subject hospitalization on 6/10/97. The subject experienced intractable nausea and vomiting that was related to the study. The event was not reported to the IRB until submission of the Report of Adverse Event signed on 10/7/97, nearly four months after the event occurred. The response letter from the IRB dated 10/24/97 failed to inform the clinical investigator that the reporting of the adverse event was not immediate as required by the Institutional Review Board Policies and Procedures.

7. **Failure to require documentation of informed consent in accordance with 50.27. [21 CFR 56.109(c)]**

   Dr. Luis E. Tenorio's subject ~~ failed to date the consent form as required by federal regulations. Dr. Tenorio received acknowledgment for "compassionate" use of a test article for the subject (no IRB study #) from the IRBs' Compliance Office dated 10/22/97.

8. **Failure to retain copies of all research proposals and supporting documents. [21 CFR 56.115(a)(1)]**

   The IRB study file for "compassionate" use of ~~~ was not found during the inspection. The file should contain documentation regarding life-time "compassionate" use for subject ~~ as noted in meeting minutes for IRB 01 on 2/2/98.

9. **Failure to prepare and maintain adequate records of continuing review activities. [21 CFR 56.115(a)(3)]**

   a. IRB personnel did not maintain a copy of the agenda for the 11/18/97 meeting of IRB 01B.

   b. IRB study ~~ is listed incorrectly in 11/95 meeting minutes under the heading of Continued Reviews That Have Not Experienced Changes or Adverse Reactions, Approved. Amendments #2, 3, and 4 were submitted to the IRB in 11/94, 2/95 and 8/95.

We have current concerns regarding the IRBs' implementations of expedited review in approvals of "compassionate use"/single use studies and emergency use situations. The University of South Florida Health Science Center Institutional Review Board was last inspected by FDA in December 1992. Similar concerns were noted in item #1 of the Form FDA 483 to Thomas G. Ferguson, Coordinator of Research Compliance, dated 12/15-18/92 regarding the 1992 inspection. Criteria for expedited review are described in Appendix D in the FDA Information Sheets (Federal Register Vol. 46, No. 17 Tuesday, January 27, 1981, 46 FR 8980).

The term "compassionate use" is often used to refer to the provision for use of investigational drugs outside of an ongoing clinical trial to a limited number of subjects who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or the Department of Health and Human Services (DHHS) regulations. The FDA human subjects regulations allow for a test article to be used in emergency situations without prior IRB approval.

In emergency use situations, the IRB must either convene and give 'full board' approval of the emergency use or, if the conditions of 21 CFR 56.102 (d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval. Prior notification of the IRB without full IRB review and approval of the use of the test article is not to be interpreted as expedited approval for the emergency use. Instead, the notification is to allow the IRB to ensure that full reporting of the emergency use to the IRB occurs within five days of use. Further use of the test article requires full IRB review and approval. Protocols termed "compassionate" receive full board review prior to implementation unless circumstances warrant emergency use. The IRB should consider whether or not to define in the written procedures how to deal with single subject non-emergency requests.

We note that procedures for expedited review, emergency use, and "compassionate" studies were revised during the inspection. Please explain how and when these procedures will be implemented.

The Chair of IRB 01B indicated that the Chair of IRB 01 performs all review of emergency use or "compassionate," single subject requests. Please explain why meeting minutes of IRB 01B also list single use or compassionate use studies.

We note the IRBs intend to use alternate members in the future. We remind you that alternate members are to be appointed in advance and listed on the IRB roster noting the member(s) for whom they may substitute.

The FDA investigator reports that the IRBs have at least 750 active studies. Nearly 5,000 study numbers have been assigned by the IRBs. The FDA investigator found there was no complete and accurate tracking system in place at the time of inspection.

The manual accounting of studies is inadequate to assure that continuing reviews are conducted at the appropriate intervals. There is no log of all the studies. Single Use, Compassionate or Emergency Use studies are not assigned IRB study numbers. No periodic reports are generated to assure proper tracking. There is no control system to identify when IRB files are removed from the central file location. The IRB agendas are generated by the investigator packets received by the IRB.

Please indicate when the electronic system will be available and reliable for use to track approaching deadlines for continuing review of studies. Please explain how the IRB will track the location of hardcopy files removed from the central file. Please explain how Single Use, Compassionate or Emergency Use studies will be tracked.

We note that the written standard operating procedures (SOPs) for the IRB are being revised in response to the inspection. Please inform us of the expected time frames for completion of the changes and forward a copy to us for review. Your file will remain open until we receive a copy of your finalized version of the SOPs, and they are deemed adequate. We enclose the "FDA IRB Information Sheets" to assist you in implementing the changes necessary to bring the IRB into compliance with applicable standards. Pages 136-143 of the enclosure provide a guide to ensure that all required elements are included in your written procedures.

This letter is not intended to be an all-inclusive list of deficiencies with the IRB. The IRB is responsible to adhere to each requirement of the law and relevant regulations.

Based upon the demonstrated deficiencies in organizational guidelines, operational procedures, recordkeeping practices, the lack of improvement in a significant deficiency noted during the 1992 inspection, and demonstrated deficiencies regarding continuing review, it appears that your procedures are inadequate to protect the rights and welfare of human subjects of research. As described in section 56.120 of the regulations, failure to make adequate corrections may result in regulatory action being initiated by the Food and Drug Administration. These actions include, but are not limited to, withholding approval of new studies, direction that no new subjects be added to ongoing studies, termination of ongoing studies, and notification of State and Federal regulatory agencies.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken or plan to take to bring the procedures of your Institutional Review Board into compliance with FDA requirements. If corrective action cannot be completed within 15 working days, state the time within which the corrections will be completed.

Should you have any questions or comments about the contents of this letter or any aspects of operation and responsibility of a review board, you may contact Debra Bower, Consumer Safety Officer, Bioresearch Monitoring, Division of Inspections and Surveillance, at (301)827-6221.

Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448, Attention: Steven A. Masiello, HFM-600.

Sincerely,

Steven A. Masiello
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosures

Form FDA 483, List of Inspectional Observations, 1998
FDA Information Sheets (includes CFR Parts 50 and 56)
Form FDA 483, List of Inspectional Observations, 1992